



## Case studies of the actual application of Anaxomics technologies to add value to Biopharma discovery

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# Business case: MoA and Safety (1)

## Situation

Some compounds of the class orexin receptor antagonists tend to produce cardiotoxicity.

A client with new NCE in same class had to discuss with regulatory agencies that cardiotoxicity was not likely to occur for their product.

## Anaxomics Strategy

Client's new compound had different target profile from other drugs in class. Besides orexins A and B, the other compounds in class (or their metabolites) had different additional targets from client's compound.

Anaxomics created the biological network around known targets of all compounds, including 1000+ nodes and millions of interactions. We developed a model that explained the observed behaviour of more than 100 known drugs whose targets were contained in the network.

## Solution and Practical Use

Using the same network and model that explained the behaviour of known drugs, we predicted that the Client's compound was not likely to produce cardiotox, because of its different target profile. **After analyzing how the mechanistic model was build, regulatory agency agreed that the Client's compound was not likely to produce cardiotox, because targets and pathways involved where different.**

# Business case: MoA and Safety (2)

## Situation

A company is exploring a NCE which is a dual inhibitor of enzymes neprilysin (NEP) and aminopeptidase-N (APN), involved in pain. Metabolites of the compound are known to bind to 3 other targets not involved in pain pathways. Besides, company has microarray and proteomics data in response to drug and metabolites exposure. The company wants to explore future clinical safety and new indications of the compound.

## Anaxomics Strategy

Anaxomics created the biological network around known targets of compound and metabolites, including 1000+ nodes and millions of interactions. We developed a model that explained the observed behaviour of more than 100 known drugs whose targets were contained in the network, and that explained the behaviour of the additional microarray proteomics information.

## Solution and Practical Use

Using the same network and model that explained the behaviour of known drugs, we predicted that the Client's compound was likely to produce cardiotox, specifically QTc prolongation problems, caused by the interaction of metabolites with non-pain targets. **Client tested compound extensively in murine cardiotox models and found out potential cardiotox. NCE was discarded.**

# Business case: MoA and Safety (3)

## Situation

A company is developing a new compound for Alzheimer Disease, currently in Phase III. Clinical data shows some risk of hepatotoxicity. Client wants to understand why this is happening, and if patients at risk can be discriminated. Client has preclinical data and microarray data in humans and animals (rats and dogs).

## Anaxomics Strategy

Anaxomics created the biological network around known targets of compound, known proteins involved in AD and known proteins and pathways in hepatotox. The resulting map included 1000+ nodes.

Also, we created different maps for different species, and for different types of patients (those with hepatotox vs those without hepatotox).

## Solution and Practical Use

We developed a model that explained the mechanistic relationship between drug's targets and hepatotoxicity only in certain conditions.

**Biomarkers for hepatotox were hypothesized and are currently being tested in clinical setting. If hepatotox is confirmed, Client wants to develop an accompanying diagnostic biomarker test.**

# Business case: MoA and Safety (4)

## Situation

Anaxomics has predicted potential negative effects of a certain very common prescription drug and of other drugs of the same family.

## Anaxomics Strategy

Anaxomics created the biological network around neurodegenerative diseases pathways, and simulated effects of a collection of unrelated drugs. Unexpectedly, we predicted that a very common drug, used widely for a number of indications, was mechanistically related with amyloid protein accumulation.

We tested in vitro and in vivo our predictions in animal models.

## Solution and Practical Use

Experimental results show a consistent dose-dependent response of the compound studied and of other similar compounds of the same family in provoking amyloid protein accumulation in brain in mice.

**This could have further epidemiological consequences in humans.**

# Business case: MoA and Indications (5)

## Situation

A company is developing a series of new compounds for diabetes, with a new MoA based on targetting 2 completely different pathways in a very innovative approach. For obtaining the IND, they are requested to conduct systems biology and predictive studies to explain the new MoA.

## Anaxomics Strategy

Anaxomics created the biological network around the targeted pathways of compounds, and around diabetes pathways.

Anaxomics modelling proved a synergistic mechanistic interaction of both pathways for improving diabetes biomarkers.

## Solution and Practical Use

**Client used our network and model in support of their claims for obtaining an IND for their compounds.** Information is currently under analysis by regulatory agencies.

# Business case: MoA and Safety (6)

## Situation

A European VC wants to invest in a small pharma that has developed 2 compounds: A and B as HDAC inhibitors. They want to select only one compound to move forward, mainly based on the better safety profile.

## Anaxomics Strategy

Anaxomics created the biological network around HDAC isoforms and other known targets of compounds. The resulting map included 1000+ nodes.

Anaxomics develops a mechanistic model that explains actually observed safety profile of compounds in HDAC class, with an accuracy level of > 80%.

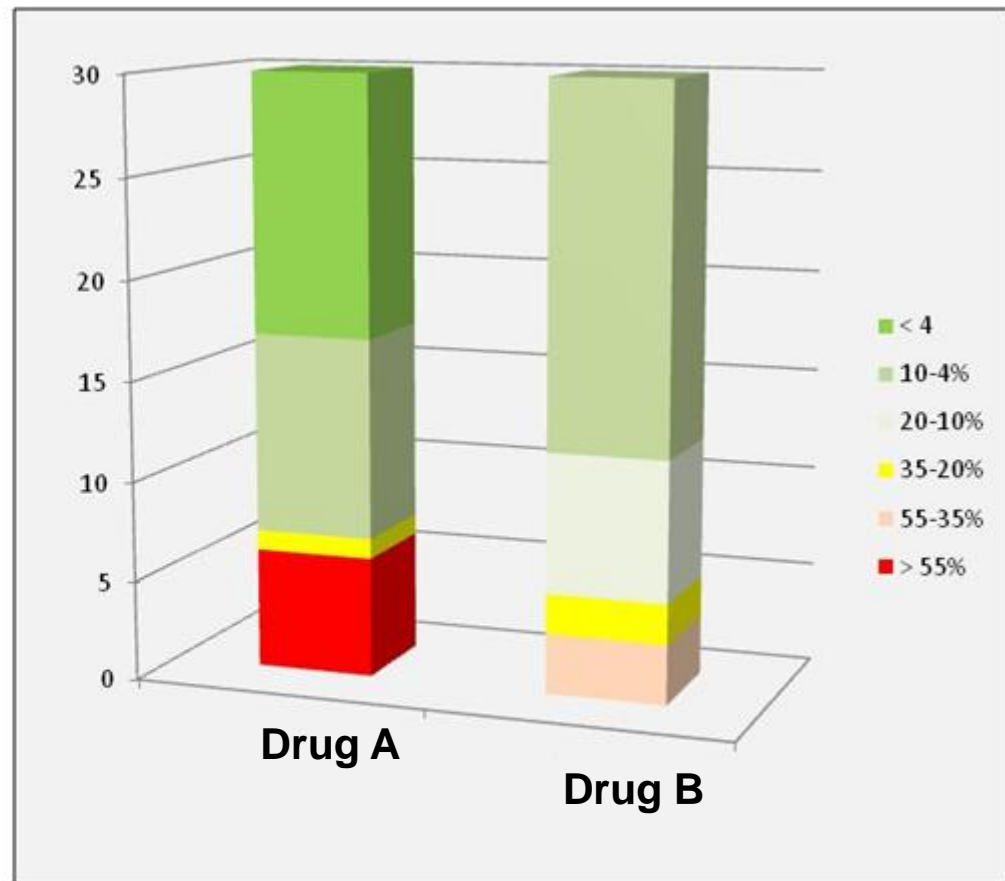
Anaxomics conducts the comparison of the safety profile between the 2 compounds, and compares them with the class

## Solution and Practical Use

We developed clinical safety profile of compounds A and B, thus **helping Client to take informed decisions** (see following figures).

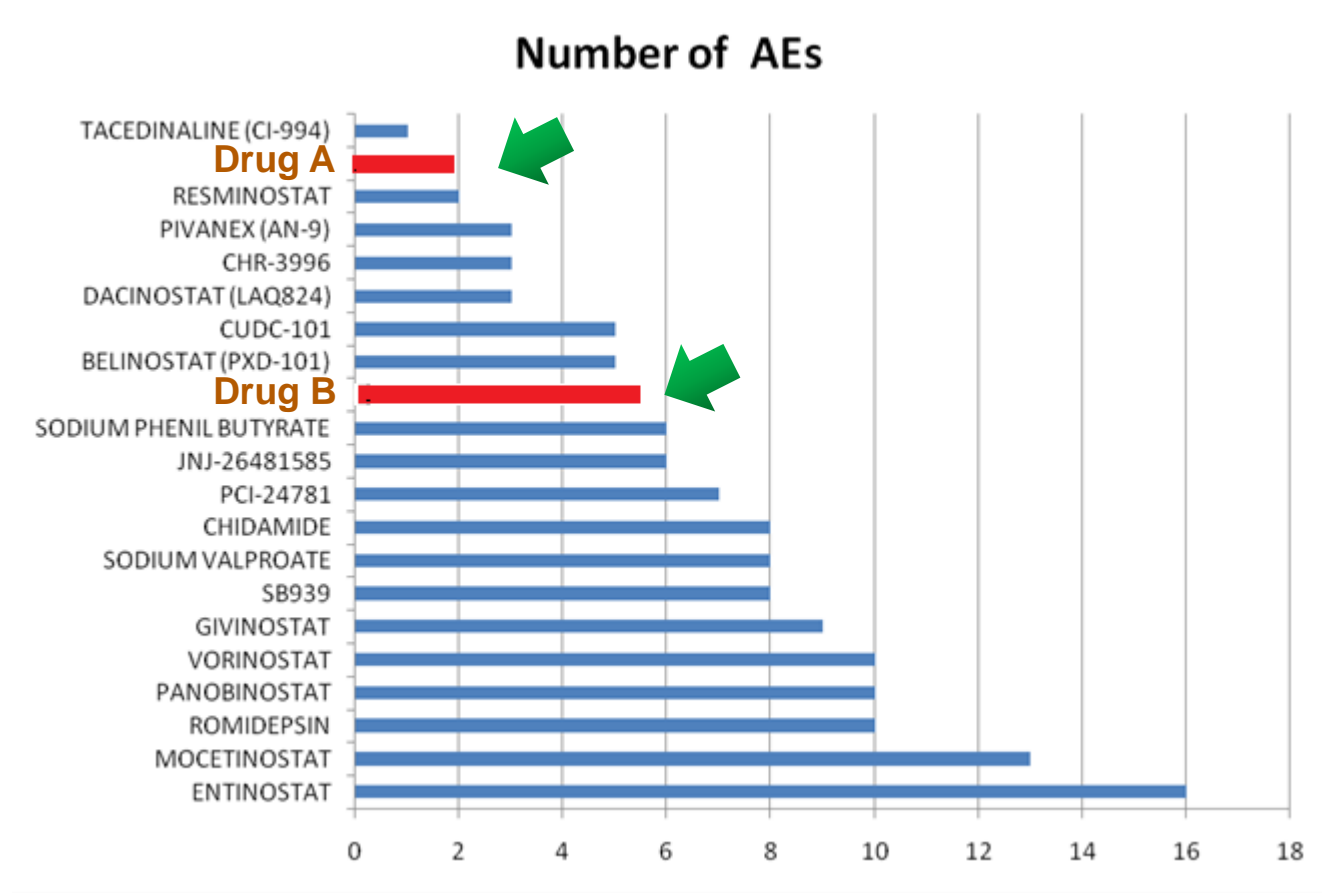
## Example: Safety profile of Drug A and Drug B based on their targets

| ADVERSE EVENTS   | Drug A | Drug B |
|------------------|--------|--------|
| ANEMIA           | 78%    | 8%     |
| ANOREXIA         | 91%    | 14%    |
| CONSTIPATION     | 0%     | 10%    |
| CRAMPS           | 3%     | 6%     |
| DEPRESSION       | 5%     | 8%     |
| DIARRHEA         | 90%    | 45%    |
| DYSPEPSIA        | 3%     | 8%     |
| DYSPNEA          | 4%     | 5%     |
| EMESIS           | 76%    | 33%    |
| FATIGUE          | 88%    | 18%    |
| FEVER            | 5%     | 5%     |
| FLATULENCE       | 6%     | 6%     |
| FLUSHING         | 3%     | 6%     |
| HEADACHE         | 1%     | 5%     |
| HEARTBURN        | 8%     | 6%     |
| KALEMIA_HYPO     | 3%     | 45%    |
| LEUKOPENIA       | 3%     | 5%     |
| LYMPHOPENIA      | 3%     | 5%     |
| NATREMIA_HYPO    | 1%     | 6%     |
| NAUSEA           | 95%    | 12%    |
| NEUTROPENIA      | 5%     | 5%     |
| PAIN             | 3%     | 5%     |
| QTc PROLONGATION | 0%     | 10%    |
| SOMNOLENCE       | 6%     | 16%    |
| TACHYCARDIA      | 4%     | 38%    |
| TASTE_DISORDERS  | 5%     | 8%     |
| TENSION_HYPO     | 5%     | 16%    |
| THROMBOCYTOPENIA | 21%    | 5%     |
| URICEMIA_HYPER   | 3%     | 5%     |
| WEIGHT_LOSS      | 5%     | 22%    |



Global positive predictive value >90%

# Positioning of Drug A and Drug B in comparison with other molecules in class.



# Business case: MoA and Efficacy (7)

## Situation

Same previous company with HDAC inhibitors wanted to explore the use of the selected compound in certain cancer type, in combination with a standard of care in this indication.

## Anaxomics Strategy

Again, Anaxomics created the biological map and model around drug targets and mechanisms and pathways related with targeted cancer type, and developed the model that explained known data about efficacy of drugs whose targets were contained in the map and model.

Specifically, Anaxomics explored the potential mechanistically synergistic effect of the client's compound and the standard of care drug.

## Solution and Practical Use

**Currently, this analysis plus other preclinical data is being used by the Client to defend in front of regulatory agencies the use of the combination in Phase II trial.**

# Business case: Drug Reprofilng in Alzheimer

## Situation

Public-private research consortium wants to conduct research in reprofiling in Alzheimer Disease.

## Anaxomics Strategy

Anaxomics created the biological network around known AD and related dementias pathways and molecular effectors (see following figures).

## Solution and Practical Use

Some drugs – currently used for other non-SNC indications - are identified with a possible new MoA in AD.

The ones without any prior IP on CNS and which are able to cross BBB are selected for in vitro and in vivo experiments.

3 Drug combinations show promising results in in vitro and in vivo experiments by the MoA predicted by Anaxomics.

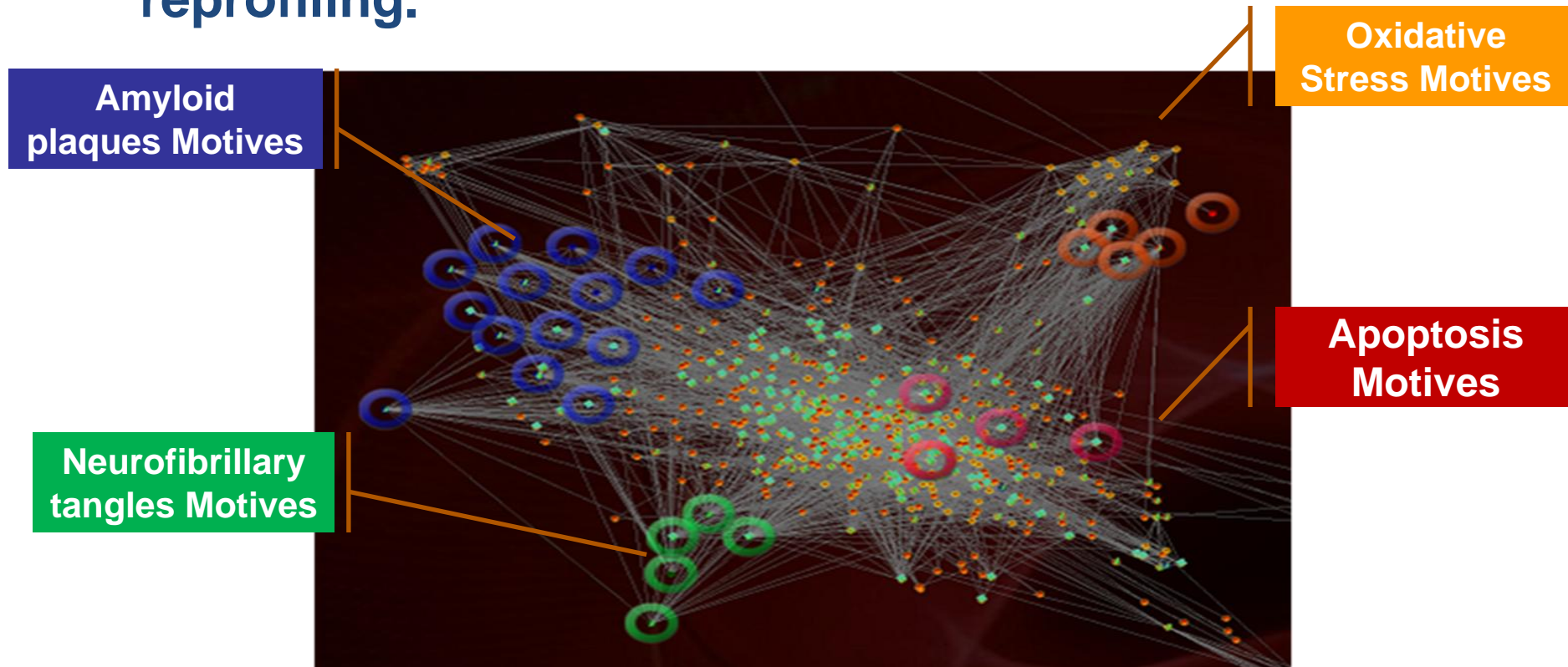
The 3 drug combinations are being fully validated in preclinical stage.

The 3 drug combinations are safe for the previous known indications

**Research consortium is patenting new compositions of matter and new uses of the selected combinations**

# Business case: Drug Reprofileing in Alzheimer

- Academic Research Consortium to develop new therapies for Alzheimer's Disease by drug reprofiling.



# Business case: Drug Reprofiling in Alzheimer

- Thanks to our technology we have identified 8 known compounds, without prior IP, with promising in vitro / in vivo results

Cutoff = 0.4

| Drug               | ANN prediction Score | AD treatments and drugs on AD clinical trials |
|--------------------|----------------------|---|
| Memantine          | 0,159                | ●   |
| Phosphatidylserine | 0,120                | ●   |
| Acaxxx             | 0,120                |   |
| Vitamin E          | 0,100                | ●   |
| Rifxxx             | 0,080                |   |
| Micxxx             | 0,080                |   |
| Phexxx             | 0,080                |   |
| Fluxxx             | 0,080                |   |
| Melatonin          | 0,080                | ●   |
| Aprxxx             | 0,080                |   |
| Rilxxx             | 0,080                |   |
| Rivastigmine       | 0,080                | ●   |
| Galantamine        | 0,080                | ●   |
| Isoxxx             | 0,060                |   |
| Bepxxx             | 0,060                |   |
| Perxxx             | 0,060                |   |
| Pimxxx             | 0,060                |   |
| Fluxxx             | 0,060                |   |
| Felxxx             | 0,060                |   |
| Estrone            | 0,060                | ●   |
| Donepezil          | 0,060                | ●   |
| Choline            | 0,060                | ●   |
| Alexxx             | 0,040                |   |
| Flunxxx            | 0,040                |   |
| Estxxx             | 0,040                |   |
| Quixxx             | 0,040                |   |
| Warxxx             | 0,040                |   |
| Thiamine           | 0,040                | ●   |
| Buspirone          | 0,040                | ●   |
| Estradiol          | 0,040                | ●   |
| Letxxx             | 0,040                |   |
| Mifepristone       | 0,040                | ●   |
| Minaprine          | 0,040                | ●   |
| Flurbiprofen       | 0,040                | ●   |
| Thioridazine       | 0,040                | ●   |
| Celecoxib          | 0,040                | ●   |

# Business case: Drug Reprofilng in Alzheimer

| Combinations |        | Predicted        |        |        | % synergism |
|--------------|--------|------------------|--------|--------|-------------|
|              |        | Drug combination | Drug A | Drug B |             |
| Rilxxx       | Bepxxx | 0,16             | 0,08   | 0,06   | 50,03       |
| Rilxxx       | Diaxxx | 0,14             | 0,08   | 0,02   | 42,90       |
| Thixxx       | Rilxxx | 0,12             | 0,04   | 0,08   | 33,39       |
| Metxxx       | Rilxxx | 0,12             | 0,04   | 0,08   | 33,39       |
| Alexxx       | Felxxx | 0,10             | 0,04   | 0,06   | 39,97       |
| Alexxx       | Bepxxx | 0,10             | 0,04   | 0,06   | 39,87       |
| Alexxx       | Micxxx | 0,10             | 0,04   | 0,08   | 19,87       |
| Alexxx       | Melxxx | 0,10             | 0,04   | 0,08   | 19,87       |
| Alexxx       | Docxxx | 0,08             | 0,04   | 0,04   | 50,02       |
| Alexxx       | Tamxxx | 0,08             | 0,04   | 0,04   | 50,02       |
| Bepxxx       | Tamxxx | 0,08             | 0,06   | 0,04   | 24,96       |
| Rilxxx       | Minxxx | 0,12             | 0,08   | 0,04   | 33,39       |
| Rilxxx       | Minxxx | 0,12             | 0,08   | 0,04   | 33,39       |

Some of the combinations also show positive results in vitro / in vivo models

# Drug Reprofile: New indications for pairs of drugs

## Situation

Mid-Pharma company has developed new molecules by co-crystallizing pairs of known drugs (for example, crystals of duloxetine+naproxen, atorvastatin+atenolol, and many others).

They want to systematically explore synergistic potentiating of therapeutic uses, and to explore new unexpected combinations.

## Anaxomics Strategy

Anaxomics created all the different biological network maps around known drug-combinations targets. We developed also individual different models for each map related with each pair of molecules. We developed individual models that explained the observed behaviour of more than 100 known drugs whose targets were included in the different networks.

## Solution and Practical Use

Anaxomics provides in 2 months a full report providing potential new indications for more than 20 combinations, with a post-hoc scientific rationale of the main ones.

**Results are presented in a readable and clear way for the client, helping them take correct decisions on which combinations align better with their portfolio strategy** (see next figures)

# Drug Reprofilng: New indications for pairs of drugs

| INDICATION         | METHODS |   |   |   | RANKING | COMMENT  | EFFECT   |            |
|--------------------|---------|---|---|---|---------|--|----------|------------|
|                    | 1       | 2 | 3 | 4 |         |  | CURATIVE | PALLIATIVE |
| Multiple Sclerosis | ☐       | ● |   | ✓ | ●       | The combination could show palliative effects on MS patients reducing pain and depression associated to MS. It could also minimize side effects related to the most common MS drug, IFN-beta. It could reduce the cognitive impairment associated to MS. |          | ✓          |
| Alzheimer Disease  | ☐       | ☐ |   | ✓ | ●       | The combination could be a rational complementary therapy for the treatment of AD patients with depression comorbidity. It could improve cognition and depression in AD patients.  | ✓        | ✓          |
| Lymphoma           |         |   | ☐ | ✓ | ●       | The combination could both reduce pain and depression associated to cancer patients and lymphoma growth.   | !        | ✓          |
| Neoplasm           |         |   | ☐ | ✓ | ●       | The combination could both reduce pain and depression associated to cancer patients and neoplasm growth. However, a combination with a selective COX2 inhibitors could be more effective.  | !        | ✓          |
| Osteoporosis       | ☐       | ○ |   |   | ●       |  |          |            |
| Depression         |         |   |   | ✓ | ●       | The combination may be an effective therapy in the management of patients with major depression.   | ✓        | ✓          |
| Pain               |         |   |   | ✓ | ●       | The dual combination could be effective in reducing pain but it could increase bleeding risk.  |          | ✓          |

METHOD1 Topological Analysis to Effector Proteins  
 METHOD2 Modeling Analysis  
 METHOD3 Topological Analysis to Drug Targets  
 METHOD4 Expert Documentation Search

☐ Score  
 ● Ranking (+ → -)  
 ✓ Bibliographic Reference  
 ✓ ! ✗ Type of effect (+ → -)

# Business case: Safety Biomarkers

## Situation

Nucro-Technics, a leading Pharmaceutical contract support organization based in Toronto, that provides advanced services to the biopharma industry, and Anaxomics form an alliance to jointly conduct research in identifying new biomarkers for early prediction of clinical safety profile of drugs in development.

## Anaxomics Strategy

Hepato-, cardio- and nephrotoxicity biological maps are constructed, and new metabolites or combinations of them that can be specifically attributed to clinical safety are identified by using Anaxomics systems biology approach. Those metabolites are then validated by Nucro-Technics by using advanced laboratory procedures.

## Solution and Practical Use

The research project is still ongoing, but early results show a promising set of newly identified biomarkers that can become essential for developing a quick and accurate preclinical safety module to be used in early stages by biopharma companies all over the world.

# Business Case: Regulatory requirements

## Situation

A Biotech Company requested Anaxomics to write the corresponding chapters in their IND / IMPD submission regarding Predictive Medicine by using Safety Analysis embedded in the Therapeutic Performance Mapping Systems service.

## Anaxomics Strategy

In connection with regulatory requirements of EMEA and the FDA, Anaxomics provides ways to improve the consistency transparency and communication of benefit-risk assessments, through structured and qualitative approaches. Specifically, Anaxomics analysis was used to compile part of the 9A section: "Guidelines on Pharmacovigilance for Medicinal Products for Human Use".

## Solution and Practical Use

Thanks to Anaxomics support, Company established solid relationships with regulatory agencies, paving the way for further approvals, and raising the threshold of innovation for direct competitors.

# Business Case: Solutions in Nutraceuticals

## Situation

A nutraceuticals company specialized in high-protein diets requests Anaxomics to provide scientific background to support their claims in using their diet for diabetic patients.

The diet is based in high-protein-low-carbon functional food, so the patient is maintained close to Ketosis status.

## Anaxomics Strategy

Anaxomics creates the protein map related with ketosis, and establishes the relationship between the ketosis and diabetes map (among other conditions).

Anaxomics generates new hypothesis for the nutraceuticals company to pursue their quest of scientific claims for their product.

## Solution and Practical Use

Anaxomics delivers 2 scientific articles and several communication to congresses.

# Business Case: Solutions in Cosmetics

## Situation

A number of cosmetic companies are exploring the use of growth factors like epidermal growth factor (EGF), fibroblast growth factor (FGF), interleukins (IL), and the similar, or even human growth hormones (hGH) to stimulate growth of the human skin cells for cosmetic uses.

But there is a need to find optimal combinations of these compounds to:

- minimize the quantity used, as they are expensive
- find synergistic combinations that maximize the effect
- combine them with other cosmetic active compounds

## Anaxomics Strategy

Starting from the human skin interactions map, we have developed a network model that reproduces biochemical behaviour in the skin (metabolic, signalling and growing), and have created a "virtual mixer" that allows to simulate combinations of compounds to maximize desired effects.

## Solution and Practical Use

Some of the predicted combinations have been tested in vitro and in clinical trials with optimal results.

# Business Case: Solutions in Well-Being

## Situation

Companies working in the area of functional food make strong efforts to:  
justify mechanistically their health claims  
find new properties for their products

One of the new ways to confer desired properties to foods is in the area of "foods that produce well-being".

Well-being is a status that is biochemically mediated by the activation of certain metabolic and signalling routes (dopamine, serotonin, oxytocin, etc).

Some food compounds can have effect over these routes and produce pleasant sensations by mechanisms of action not yet clearly understood (for example, chocolate products).

## Anaxomics Strategy

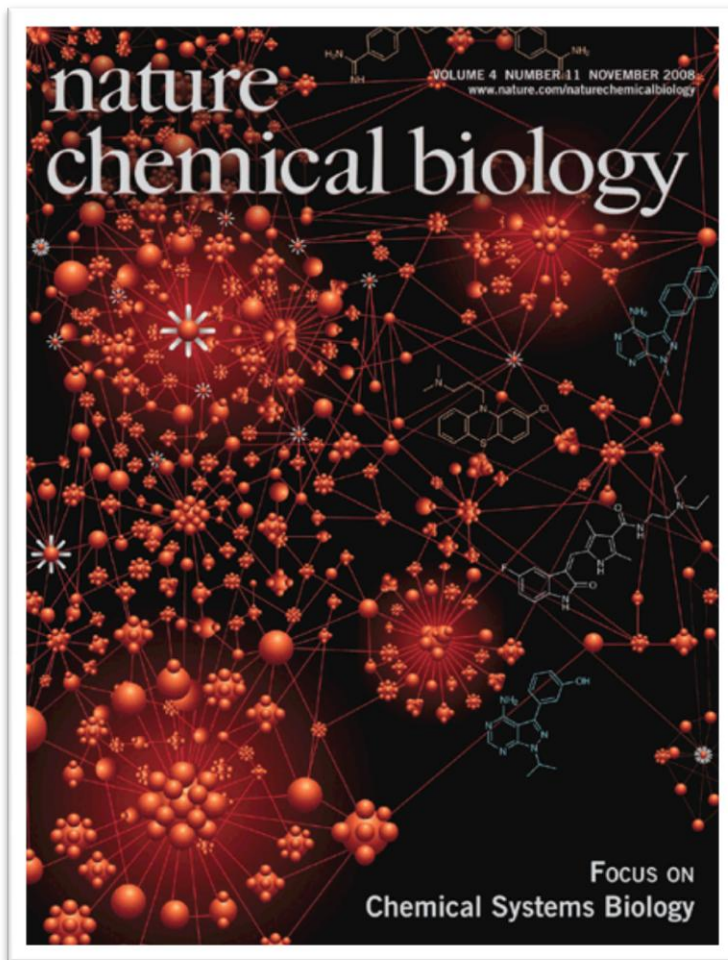
We are currently working with certain nutraceuticals companies to create a platform to allow ad-hoc design of food products with desired properties.

## Solution and Practical Use

Design new products with desired new properties related with well-being, providing at the same time enough rationale of action.

# STRONG SCIENCE BEHIND ANAXOMICS

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Nature Chemical Biology - Nov. 2008  
(Cover) Artistic representation of human interactome. Produced using the analysis package AxPathBuilder of Anaxomics Biotech.